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(54) Title: METHOD FOR TREATING MYOFASCIAL PAIN SYNDROME

(57) Abstract

Pain associated with myofascial pain syndrome is treated by administering to a muscle of a patient afflicted with the syndrome a therapeutically effective amount of a chemodenervating agent which selectively blocks the release of acetylcholine at motor endplates causing relaxation and atrophy of the treated muscle. The treatment produces a localized, sustained analgesic effect at the site of the myofascial pain source.

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METHOD FOR TREATING MYOFASCIAL PAIN SYNDROME

Background of the Invention

The invention relates to a method for treating the symptoms of myofascial pain syndrome by specific partial, reversible chemical denervation of the myofascial pain source.

Myofascial pain syndrome is a chronic pain condition with often widespread pain complaints, trigger points and tender points. "Trigger points" in particular are characteristic of the syndrome. A trigger point is an area which, when pressed by a pressure gauge or finger, produces pain in a distribution in which the symptoms appear to occur. Tender points are areas of the muscle that, when pressed, create pain at the site of compression. Tender points differ from trigger points in that pressure on a tender point does not reproduce or "trigger" the distribution of pain associated with the original complaint. Muscles afflicted with myofascial pain often demonstrate tender tight bands upon palpation. The pain is usually localized to the muscular area and is not associated with tenderness over bone articulation or anatomic areas occupied by tendon structures.

Myofascial syndrome sometimes is misdiagnosed as fibromyalgia or fibrositis syndrome. These terms in older literature may have been interchangeable with chronic muscular pain; therefore, myofascial pain sometimes can be viewed as localized fibromyalgia. Fibromyalgia is a generalized syndrome characterized by tenderness within diffuse distribution of muscle groups and associated systemic complaints such as sleep

disturbances, generalized fatigue, chronic headaches and irritable bowel symptoms. These characteristics distinguish it from myofascial pain syndrome. Localized fibromyalgia also has been referred to as "fibrositis", which may be considered almost the same as fibromyalgia.

A palpable trigger point is essential to the diagnosis of myofascial pain syndrome. There are specific features characteristic of the trigger point, including:

1. Pain referred from the trigger point is usually described as a subcutaneous location with slightly blurred edges;
2. Several muscles (including the deltoid, gluteus maximus, oseratus posterior/inferior) refer pain locally in the immediate vicinity of the trigger point;
3. Trigger points in the limb muscles refer pain distally rather than proximally;
4. Pain occurring in certain muscles is referred into adjacent joints, occasionally mimicking arthritis;
5. Aching pain in the pltysma muscle secondary to myofascial causes is described as a "prickling" sensation; and
6. Trigger points may refer hypesthesia (numbness) or anesthesia instead of pain.

The pain patterns referred by the trigger points generally are predictable.

Myofascial pain syndrome often is associated with reduced range of motion. The pain complaint can be reproduced by digital pressure or by needle penetration f the trigger point. Pain is thought to be caused by unusual tension, tone and afferent receptors within

muscle which carry the impulse perception of pain. These pain receptors have been termed "nociceptors." Nociceptors are microanatomic elements within muscle which sense stretch and perhaps pain.

Myofascial pain syndrome can be a cause of post-operative pain. For example, myofascial pain syndrome may arise after temporomandibular joint surgery or acoustic neuroma surgery. Myofascial pain is specifically distinguishable from pain arising from joint and bone by the absence of arthritis or other forms of joint pathology, as demonstrated on routine radiographs, computerized tomography (CT) or magnetic resonance imaging (MRI). The trigger points in myofascial pain are clearly within the palpable body of the muscle. Tight bands are palpable in muscles demonstrating this particular syndrome, which often are associated with trigger points. Electrophysiologic measurement of changes at the trigger points have been attempted, but the results have not been consistent. Durett et al., Am J Phys Med Rehabil, 70(3):154-156 (1991); Fricton et al., Arch Phys Med Rehabil, 66(5):314-317 (1985)

The following represents a summary of clinical criteria for diagnosing myofascial pain syndrome caused by active trigger points. The five major criteria include:

1. Regional pain complaint;
2. Pain complaint or altered sensation in expected distribution of referred pain from a myofascial trigger point;
3. Taut band palpable in an accessible muscle;
4. Exquisite spot tenderness at one point along the length of a taut band; and
5. Some degree of restricted range of motion.

Minor criteria which can be used to support the diagnosis include:

1. Reproduction of clinical pain complaint by pressure on a tender spot;
2. Elicitation of a local twitch response by transverse snapping palpation at the tender spot or needle insertion into the tender spot; and
3. Pain alleviated by elongating the muscle or injecting a tender spot.

"Muscular Pain Syndromes" by David Simmons, Advances in Pain Research and Therapy, vol. 17, Raven Press Ltd, NY (1990).

Methods currently used for pain control include local anesthetics which block transmission of impulses arising from sensory nerves; drugs which act on the central nervous system, spasmolytic agents which affect impulses from the spinal cord and spasm; and drugs which block calcium release from the sarcomere. The history of therapy for myofascial syndrome has included the use of oral analgesics such as aspirin and acetominophen, the use of non-steroidal anti-inflammatory systemic drugs such as ibuprofen, injection of a local anesthetic such as Lidocaine™, physical therapy, biofeedback, and use of sensory stimulating devices such as acupuncture or TENS units for blocking sensory pain and reducing immobilization. However, none of these therapies has been completely satisfactory in alleviating the pain associated with myofascial pain syndrome.

Summary of the Invention

The present invention relates to a method for alleviating pain and other symptoms associated with myofascial pain syndrome. The method comprises administering locally to a muscle of the patient affected by the syndrome an amount of a chemodenervating agent sufficient to alleviate the symptoms of the syndrome, wherein the chemodenervating agent deactivates impulse transmission at the neural motor endplates in the muscle. The present method provides localized relief from myofascial pain which is sustained over a period of time.

In another aspect, the invention relates to producing an analgesic effect in a patient experiencing myofascial pain by administering locally to a muscle of the patient an analgesically effective amount of the chemodenervating agent. The analgesic effect so produced is sustained for a prolonged period of time, e.g., for at least 7 days, generally for between 2 and 12 weeks, and up to as long as about 16 weeks.

Chemodenervating agents useful in the present invention are agents which specifically block release of acetylcholine from the neural motor end plates of the treated muscle. Botulinum-derived toxins are preferred agents for this purpose. Botulinum toxins block release of acetylcholine from neural motor endplates, resulting in induction of muscle fiber atrophy and muscle weakness, while retaining muscle function. Botulinum toxin affects the axonal terminal of motor nerves without having any known effect on the sensory nervous system. Within 3-4 weeks after the injection, collateral axonal sprouting accour, and new neuromuscular junctions are established in the muscle, generally ver a 10 to 12 week period. Thus, the

effects of botulinum toxin are temporary and generally run a course of about 12 weeks. After the twelve week period, normal innervation returns to the muscle and there is regeneration of muscle fiber size. Another round of treatment can be administered at this time, if necessary or desirable.

In a preferred embodiment of the present method, a therapeutic amount of a botulinum toxin preparation is administered locally to a muscle of a patient suffering from myofascial pain syndrome. The toxin preparation is injected directly into the muscle or muscles affected by the syndrome. A dose in the range of from about 5 to about 1000 IU of botulinum-derived toxin generally is effective for this purpose.

The present method provides a therapy which confers localized, sustained relief from myofascial pain over a period of several weeks or months. The method has several advantages over traditional treatments for myofascial pain. For example, it avoids the need for surgery or other invasive procedures, which carry considerable risk, and avoids the use of systemic drugs, which may have undesirable side effects. Chemodenervating pharmaceuticals, such as botulinum toxin, have few adverse effects on central nervous system functions such as cognitive reasoning, sleep patterns, appetite, affective disposition or other central nervous system functions. The present invention is distinctly different from all prior therapies in that blockage of neuromuscular transmission is the only effect of the toxin without sensory and neural effects. Reduction in tone, resting tension, and contractility in the muscle creates a secondary effect at the nociceptors resulting in decreased afferent "pain" output to the central nervous system.

Detailed Description of the Invention

The present method provides a therapeutic treatment for alleviating pain having a myofascial origin by chemically inducing denervation of a muscle or muscles. As used herein the term "myofascial" refers to a sheet of fibrous tissue (the "fascia") which encloses muscles or groups of muscles and separates muscular layers or groups. Myofascial pain syndrome is a well-defined syndrome having a characteristic set of symptoms, as set out in detail hereinabove. The term "myofascial pain syndrome" may include disorders diagnosed as localized fibromyalgia or localized fibrositis. The term is intended to include any disorders which meet the diagnostic criteria characteristic of myofascial pain syndrome. The present method involves administering to a muscle of a patient afflicted with myofascial pain syndrome an amount of a chemical denervating agent which specifically denervates the neural motor endplates in the muscle sufficient to alleviate the pain symptoms.

In another aspect, the present method produces a localized, sustained analgesic effect in a patient experiencing myofascial pain by administering locally to the afflicted muscle or muscles an analgesically effective amount of a chemical denervating agent sufficient to denervate neural motor endplates of the afflicted muscle.

Chemical denervating agents which are effective for this purpose are agents which specifically denervate neural motor endplates of the affected muscles, for example, by blocking the release of acetylcholine from the endplates. The chemical denervating agent induces a number of changes in the muscle, including diffuse muscular atrophy, elongation of muscle fiber units and

a decrease in the output of afferent impulses from the treated muscle. Injection of the denervating agent causes the treated muscle to loosen and elongate and decreases its resting tone, thereby increasing the amount of passive stretch in the muscle. Without wishing to be bound by theory, it is believed that decreasing the resting tone within muscle by chemodenervation reduces the afferent impulses transmitted to the central nervous system. Thus, the chemical denervating agent loosens muscle tone and contractility which in turn influences nociceptors in the affected muscles, thereby blocking transmission of the pain impulses. The effects of the denervating agent are sustained for a period of time which can be influenced by several factors, including the amount of the agent administered, it's extent of diffusion in the muscle, the amount and type of diluent and the patient's individual reaction to the agent. The effect in most patients will last for at least 7 days, and typically up to about 12 weeks, thus affording prolonged pain relief.

Chemical denervating agents which are particularly preferred include botulinum toxins and pharmaceutical compositions containing botulinum toxins. Botulinum toxins are a family of toxins derived from Clostridium botulinum. There are seven known serotypes of botulinum toxins, designated types A through G. Pharmaceutical grade type A toxin is commercially available from Allergan Pharmaceuticals, Inc. under the tradename Oculinum™. However, the method of the invention can be practiced using any physiologically acceptable injectable substance which interrupts neuromuscular transmission at the neuromuscular junction. Thus, other materials including proteins or

peptide subunits, hybrid or chimeric materials including the proteins or peptides, recombinantly produced materials and other various types of pharmaceutical preparations having the desired effect can be used in the practice of the invention. However, the work forming the basis of the invention was conducted using the commercially available Type A botulinum toxin material identified above.

The chemodenervating agents of this invention can be processed in accordance with conventional methods of pharmacy to produce medicinal agents for administration to patients, e.g., humans. The agents typically are employed in admixture with conventional excipients and/or diluents, i.e., pharmaceutically acceptable carrier substances suitable for injection which do not deleteriously affect the active agent. Suitable carriers include, but are not limited to, water, salt solutions, and physiologic buffers. For parenteral application, injectable sterile solutions are preferred.

The agent can be administered by any method suitable for locally administering a drug, including, for example, transdermal diffusion, transcutaneous injection, intramuscular injection or implantation of a device which releases the substance into the desired area. Transcutaneous injection directly into the afflicted muscle is the preferred method.

In a preferred embodiment of the present invention, a botulinum toxin preparation is injected into a muscle of a patient afflicted with myofascial pain syndrome. Injection of a botulinum toxin preparation into the muscle deposits a bolus of the material at the injection point which diffuses outwardly. The distance of diffusion is not clearly understood and seems to

depend upon a number of factors, including the nature and amount of diluent, the mass of the toxin molecule, the population of presynaptic receptors about the site of the injection and the physiological condition of the patient. A method for standardizing chemodenervating preparations based on the extent of their diffusion in vivo and which permits the physician to know in advance the local field of influence of a given preparation is described in copending U.S. Patent Application Serial No. 07/570,395, filed August 21, 1990 by G.E. Borodic, the teachings of which are hereby incorporated herein by reference. The active toxin binds to receptors on the presynaptic membrane, thereby preventing acetylcholine release which results in interruption of the pain signal by relaxing muscle tone and contractility.

The therapeutic and analgesic effects are achieved at dosage levels in the range of about 5 international units (IU) to about 1000 IU of the chemodenervating agent. A preferred dosage for this purpose is less than 500 IU, and most preferably about 300 IU or less. The dosage preferably is administered as a plurality of injections about the trigger point in the afflicted muscle or muscle group. An international unit is defined as the LD_{50} for a standard 20 gram white mouse. Dosages also can be administered based upon the volume of muscle denervated by a unit quantity of a chemodenervating agent as described in above-referenced patent application USSN 07/570,395. It will be appreciated that the actual preferred amounts of active compound in a specific case will vary according to the agent utilized, the particular compositions formulated and the particular site and patient being treated. Dosages for a given patient can be determined using customary, clinical practices.

Botulinum toxin preparations have been used in the past to treat certain spasmodic conditions of muscle. However, these preparations have not been indicated for the management of specific pain syndromes. The present invention demonstrates that chemodenervating agents such as botulinum toxins can be applied for the localized, sustained relief of pain resulting from myofascial pain syndrome.

The present method can be used to treat any muscle or muscle group in a patient afflicted with myofascial pain syndrome. Anatomic regions in which myofascial pain syndrome has been described include, but are not limited to, the following muscles with associated restrictions in range of motion and/or referred pain:

TABLE 1

Muscle	Restricted Movement/Referred Pain
Adductor longus	Abduction of thigh
Biceps femoris	Straight legs raising (knee extension with hip flexion)
Brachioradialis	Extension of forearm
Deltoid, anterior	Horizontal adduction of arm
Deltoid, posterior	Horizontal adduction of arm
Digastric	Refers pain to back of head, cheek, jaw, teeth, throat and front of neck
Extensor carpi radialis longus	Flexion and ulnar deviation of wrist
Extensor digitorum communis	Simultaneous flexion of fingers and wrist

Frontalis	Refers pain to the front of head
Gastrocnemius	Dorsiflexion of foot with knee straight
Gluteus maximus	Flexion at hip with knee flexed
Infraspinatus	Reaching up behind shoulder blades (full internal rotation); refers pain to back of neck
Lateral pterygoid	Refers pain to ears, temporomandibular joint, cheek and jaw
Latissimus dorsi	Flexion of arm with some trunk flexion to other side
Levator scapulae	Refers pain to back of neck
Longissimus (paraspinal)	Spinal flexion
Masseter	Jaw opening; refers pain to cheek, jaw, teeth, eye area, ears and temporomandibular joint
Medial pterygoid	Refers pain to ears and temporomandibular joint, cheek, jaw, throat and front of neck
Multifidi	Refers pain to back of neck
Occipitalis	Refers pain to back of head and eye area
Orbicularis oculi	Refers pain to eye area, cheek and jaw
Pectoralis major	Horizontal abduction of arm

Peroneus lungus	Dorsiflexion and inversion of foot
Platysma	Refers pain to cheek and jaw
Rectus femoris	Extension at the hip with flexion at the knee
Semimembranosus	Straight leg raising (knee extension with hip flexion)
Semispinalis (capitis and cervicis)	Refers pain to back of head, front of head and temporal area
Semitendinosus	Straight leg raising (knee extension with hip flexion)
Splenius (capitis and cervicis)	Refers pain to top of head, back of head, temporal area, eye area, and back of neck
Sternocleidomastoid (sternal and clavicular)	Rotation of head & neck to the same side; refers pain to top, back and front of head, eye area, temporal area, throat, neck, cheek, jaw, ears and temporomandibular joint
Suboccipital Group	Refers pain to back of head, temporal area, and eye area
Temporalis	Refers pain to back of head, temporal area, eye area and teeth
Teres major	Abduction (flexion) of arm over head with external rotation

Trapezius, upper	Lateral flexion of head to other side and rotation of head to same side; refers pain to cheek, jaw, back of neck, eye area, temporal area and back of head
Trapezius, lower	Scapular abduction with elevation
Triceps, brachii, long head	Adduction and flexion of arm with flexion of forearm
Zygomaticus major	Refers pain to front of head, cheek and jaw

The present method can be used to treat post operative myofascial pain. Myofascial pain syndrome is a principal component of post operative complaints. Traditional treatments for post-operative pain include physical therapy and non-steroidal anti-inflammatory medications, which have met with varying degrees of success. The present method is effective in post-operative relieving myofascial pain syndrome and has the advantage of providing localized refief to the pain source without administering systemic drugs which may induce unwanted side effects. An example of the efficacy of the present method in treating post-operative myofascial pain is shown in Example 2.

The invention is illustrated by the following Exemplification, which is not intended to be limiting in any way.

EXEMPLIFICATION

Case Reports and Clinical Evidence

Example 1

E.C. is an otherwise healthy 26 year old woman with a history of chronic pain. The pain has been characterized as a dull ache primarily within the region of the left shoulder that has been radiating up the posterior aspect of her skull and down towards the mid position of the low back. The pain has been very severe and has prevented the patient from maintaining gainful employment for approximately two years. She has undergone extensive evaluation at the Pain Clinic at the University of Massachusetts Hospital, Massachusetts General Hospital and Spaulding Rehabilitation Hospital. The pain was characterized as radiating to the inner aspect of her arm as well as to the region of the left portion of her neck. Although there was no posture abnormality associated with the pain, the patient felt stiffness in her neck movement when trying to make rotation excursions to the right and left. There was no evidence of dystonia or involuntary movement present.

Tense bands were palpated within her left trapezius muscle in a region of a consistent trigger point. Some generalized increase in muscle tone was also noted in this region. Pressing on the trigger point produced pain in the same region which the pain was spontaneously present. Pressing on the trigger point also produced pain in the same quality as that experienced by the patient.

Extensive neuroradiographic work-up of the cervical spine, cervical dorsal and lumbar spine failed to show any substantial bone or joint pathology.

By another examiners' inspection, the most prominent findings of the examination were several trigger points located in the left trapezius muscle. There was obvious increased tension point and probably increased "fiberous cord" noted in the region of the left trapezius when compared to the right. Also, it was felt that the left trapezius muscle had some evidence of hypertrophy compared to the contralateral side. Because of presence of hypertrophied muscle, there appeared to be increased tone in the muscle involved in a substantial pain syndrome and the diagnosis of myofascial pain syndrome warranted.

The patient previously had been previously treated with oral analgesic medications, physical therapy, neurostimulation, and trigger point injections of anesthetic (Lidocaine™) as well as biofeedback during extended hospitalization. None of these therapies was successful. Thus, experimental therapy for her pain syndrome was warranted. She was treated with botulinum A toxin (Allergan Pharmaceuticals, Inc.) receiving a dose of 40 IU at 3 injection points (a total of 120 IU) over the trigger points of pain in the left trapezius muscle. The botulinum toxin was diluted with physiologic saline to a level of 5 IU per 0.1 ml. A 25 gauge needle was used to directly inject the toxin into the trigger point.

When seen two weeks in follow-up, she reported that her pain was substantially better. However, she still experienced substantial pain. Two weeks after the initial injection a b oster injection of an additional 80 IU of botulinum A toxin was administered to the

patient. When seen approximately one month after the injections had been finalized, the patient noticed a clear increase in the range of motion of her spine, and the pain showed approximately an 80% improvement as determined by subjective evaluation. There was increased activity tolerance and she was considering returning to employment status.

Twelve weeks after the injection was given, during a period in which the biologic effects of botulinum toxin recede, she noticed an increase in pain and desired repeated injections. Her complaint of increasing pain came at a time when botulinum toxin is known to recede in its effect.

The patient underwent a second injection receiving a 5 point injection of botulinum toxin at a total dose of 100 IU over the left trapezius muscle. During the period of therapy, the patient was able to increase her activity to part-time employment and increase her demands of physical therapy.

Her physical therapist noticed a clear improvement in her ability to function and noted that there had been clear progress after the injections. The patient noticed increased strength in her muscles and experienced less headache pain.

Two months after the initial set of injections, her physical therapist, indicated that E. C. demonstrated decreased upper trapezius and cervical paraspinal muscle spasms, decreased sensitivity to massage and 20% increase in cervical range of motion. She reported decreased pain and increased neck flexibility.

Example 2

LF is an unfortunate 36 year old woman with a 15 year history of temporomandibular joint disease and chronic pain along the masseter and temporalis muscles.

Fifteen years prior to evaluation she noted increased immobility of the jaw associated with pain and jaw opening and closing and tenderness along each side of the face. The left side was originally thought to be worse than the right. She was diagnosed as having temporomandibular joint (TMJ) dysfunction with subluxation of the joint and was treated with surgical orthoplasty meniscusectomy and condyle resection.

She continued to have difficulty with opening and closing her jaw after the surgical procedures and for this reason, several years later, a surgical procedure to place prosthetic joints on both sides was performed. After the surgical procedure progressive spasms and deviation of the jaw ensued. Further surgical revision was performed subsequent to the original operation to correct prosthetic joint loosening. The jaw continued to exhibit considerable pain and immobility after these surgical procedures. The TMJ remained tender as well as the muscle itself. There were tender points over the masseter and temporalis muscle and tenderness over the temporomandibular joint as well as increased tone in the entire muscle. She was diagnosed as having post-surgical myofascial pain syndrome and was injected with 60 IU of botulinum toxin into the masseter and temporalis muscles as a trial.

Several days after the injections she noted substantial improvement in her pain and reported that her jaw felt looser. This gradually improved over a 2 - 3 week period in which she noted increased ability to open the jaw and diminishing pain. The patient stated that the pain was better than at any time in the past 4 years.

Equivalents

Those skilled in the art will recognize, using no more than routine experimentation, many equivalents to the specific embodiments recited herein. Such equivalents are intended to be encompassed by the following claims.

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CLAIMS

1. A method for alleviating the symptoms associated with myofascial pain syndrome in a patient for a sustained period of time comprising administering locally to a muscle of said patient which is afflicted with the syndrome an amount of a chemical denervating agent which blocks acetylcholine release at the neuromuscular junction of the affected muscle thereby providing sustained alleviation of said symptoms for said time period.

2. The method of Claim 1 wherein the denervating agent has the effect of inducing atrophy, causing elongation of muscle fiber units and reducing afferent output from said muscle.

3. The method of Claim 2 wherein the denervating agent comprises a botulinum toxin.

4. The method of Claim 1 wherein the denervating agent is administered by transcutaneous injection directly into the afflicted muscle.

5. The method of Claim 4 wherein the amount of the agent injected is in the range of from about 5 to about 1000 international units.

6. A method for producing a local, sustained analgesic effect in a patient experiencing myofascial pain comprising administer-ing locally to a muscle of said patient which is afflicted with said pain an analgesically effective amount of a chemical denervating agent sufficient to denervate neural motor endplates of the affected muscle.

7. The method of Claim 6 wherein the chemodenervating agent is a botulinum toxin.

8. The method of Claim 6 wherein the agent is administered by transcutaneous injection directly into the afflicted muscle.

9. The method of Claim 8 wherein the amount of the agent injected is in the range of from about 5 to about 1000 international units.

10. The method of Claim 6 wherein said myofascial pain reults from surgery.

11. The methof of Claim 10 wherein said surgery is temporomandibular joint surgery or acoustic neuroma surgery.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 94/00626

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61K37/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	THE NEW ENGLAND JOURNAL OF MEDICINE vol. 324, no. 17 , 25 April 1991 pages 1186 - 1194 JOSEPH JANKOVIC ET AL. 'THERAPEUTIC USES OF BOTULINUM TOXIN' see the whole document	1-9
X	BRITISH MEDICAL JOURNAL vol. 298, no. 6667 , 21 January 1989 pages 136 - 137 ROGER C HUMPHRY 'BOTULINUM TOXIN:A NEW ALLY OF AN OLD ADVERSARY' see the whole document	1-9

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
25 April 1994	20 -05- 1994

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Rempp, G

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DOCUMENTA OPHTALMOLOGICA vol. 72, no. 2 , June 1989 pages 189 - 198 ERMANNO MANNI ET AL. 'EFFECT OF BOTULIN TOXIN ON EXTRAOCULAR MUSCLE PROPRIOCEPTION' see the whole document	1-9
X	PHARMACEUTISCH WEEKBLAD vol. 127, no. 39 , 25 September 1992 pages 1037 - 1041 E.H.H. WILTINK ET AL. 'BOTULINE:EEN TOXINE ALS THERAPEUTICUM' see page 1038, right column, line 1 - page 1039, right column, line 5	1-9
X	MICROBIOLOGICAL REVIEWS vol. 56, no. 1 , March 1992 pages 80 - 99 EDWARD J. SCHANTZ ET AL. 'PROPERTIES AND USE OF BOTULINUM TOXIN AND OTHER MICROBIAL NEUROTOXINS IN MEDICINE' see page 83, right column, line 60 - page 85, left column, line 29	1-9
X	JOURNAL OF NEUROLOGY vol. 239, no. 1 , January 1992 pages 16 - 20 PETER HAMBLETON 'CLOSTRIDIUM BOTULINUM TOXINS:A GENERAL REVIEW...' see page 19, left column, line 13 - line 48	1-9
X,P	US,A,5 183 462 (GARY E. BORODIC) 2 February 1993 cited in the application see column 4, line 50 - column 10, line 14	1-9
E	US,A,5 298 019 (GARY E. BORODIC) 29 March 1994 cited in the application see column 4, line 54 - column 10, line 18	1-9
A	US,A,5 053 005 (GARY E. BORODIC) 1 October 1991	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/00626

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark : Although claims 1-11 are directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter nal Application No
PCT/US 94/00626

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US-A-5183462	02-02-93	US-A- 5298019	29-03-94
US-A-5298019	29-03-94	US-A- 5183462	02-02-93
US-A-5053005	01-10-91	NONE	